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COMPLETE SPECIFICATION

Bismuth Iodide Complexes and Process for the Manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel bismuth iodide complexes and a process for the manufacture thereof. More particularly, the invention is concerned with bismuth iodide complexes of 2-dehydro-emetine [otherwise known as 2 - (6¹,7¹ - dimethoxy-1¹,2¹,3¹,4¹ - tetrahydro - *iso*quinolyl - methyl)-3 - ethyl - 9,10 - dimethoxy - 1,4,6,7-tetrahydro - 11bH - benzo[a]quinolizine] and with a process for the manufacture thereof. It will be appreciated that the term "2-dehydro-emetine" used herein comprehends the racemic compound and each of the optical antipodes particularly (—) 2-dehydro-emetine.

The novel (2-dehydro-emetine)/(bismuth iodide) complexes provided by the invention are bismuth complexes of the empirical formula $C_{29}H_{38}O_4N_2,xBiI_3,yHI$ in which both x and y have values ranging from 0.7 to 2.0. They have outstanding chemotherapeutic usefulness in the control of amoebic dysentery and bilharziasis. They may be used in the form of pharmaceutical preparations. Unlike 2-dehydro-emetine itself, which is unsuitable for oral administration because of the occurrence of undesired side-effects, the complex compounds of the invention can be taken by mouth. Administration in capsules which are resistant to the gastric juice has been found to be especially advantageous.

According to the process of the invention, the foregoing complexes are manufactured by reacting 2-dehydro-emetine or an acid addition salt thereof with a bismuth iodide complex salt which contains the anion $[BiI_4]^-$.

Especially useful bismuth iodide complex salts are the alkali-metal bismuth iodides (such as potassium bismuth iodide) or ammonium bismuth iodide.

An acid addition salt of 2-dehydro-emetine with a weak acid, for example an aliphatic carboxylic acid such as formic acid, acetic acid, propionic acid, tartaric acid, ~~oxali~~ oxalic acid, lactic acid or the like, is preferably used. An acid addition salt involving hydroiodic acid is especially suitable where a salt involving an inorganic acid is required. The dihydrochloride or 2-dehydro-emetine, that is an acid addition salt involving a strong acid, can also be used, but this has the disadvantage that undesired anionic impurities (chloride ions) will be contained in the end product.

It is especially convenient to react the acetate of 2-dehydro-emetine with the bismuth iodide complex salt. The acetate can, if desired, be formed *in situ* by introducing the free base (obtained, for example, from the dihydrochloride) into acetic acid and then adding the bismuth iodide complex salt.

If an alkali-metal bismuth iodide is used as the bismuth iodide complex salt this can, if required, also be formed *in situ* from bismuth oxide (Bi_2O_3) and an alkali-metal iodide.

The following examples illustrate the process provided by the invention.

EXAMPLE 1.

25.0 g of racemic 2-dehydro-emetine dihydrochloride (moisture content 2.3%) and 40 g of ice were suspended in 160 ml of water. After the addition of 11 ml of 30% sodium hydroxide solution the reaction mixture was extracted three times with chloro-

[Price 4s. 6d.]

form. The residue obtained upon evaporation of the combined chloroform extracts was dissolved in 125 ml of glacial acetic acid. To the resulting solution there was rapidly added a solution of 103 ml of saturated potassium iodide solution, 10.3 g of bismuth (III)/oxide and 255 ml of glacial acetic acid at 25° C and the mixture was stirred for a further hour. An orange-red precipitate formed which was filtered off, washed several times with water and dried under reduced pressure at 45° C. The so-obtained mass was stirred once more with a solution of 50 ml of ethanol in 50 ml of water. After drying under reduced pressure (12 mm Hg) at 45° C there was obtained 51.6 g of an orange-red powder of the following composition: $C_{29}H_{38}O_4N_2$,1.16BiI_3,2HI.

EXAMPLE 2.

The base obtained from 100 g of racemic 2-dehydro-emetine dihydrochloride was dissolved in 600 ml of glacial acetic acid and treated at about 40° C while stirring with 900 ml of a potassium bismuth iodide solution which had been obtained by dissolving 10 g of bismuth oxide in 100 ml of a saturated aqueous potassium iodide solution at room temperature, dilution of this solution with 250 ml of glacial acetic acid and filtration. After addition of the potassium bismuth iodide solution the mixture was further stirred for about 1 hour and then filtered. The vermilion residue remaining in the filter was subsequently washed portionwise with 300 ml of water and then dried at 50° C in a vacuum drying-oven. 223 g of substance were obtained.

For purpose of homogenisation, the product was made into a paste by stirring together with 500 ml of 50% aqueous ethanol for 1 hour at 40° C. Then it was filtered and dried to constant weight in a vacuum drying-oven at 50° C. There were thus obtained 178 g of the vermilion complex compound with the composition $C_{29}H_{38}O_4N_2$, 0.85 BiI_3,2HI.

EXAMPLE 3

The base obtained from 1 g of (−) 2-dehydro-emetine dihydrobromide was dissolved in 5.2 ml of glacial acetic acid and treated with stirring at about 40° C with 7.8 ml of potassium bismuth iodide solution, which had been prepared in the manner set forth in Example 2. Stirring was continued for 1 hour. The resulting orange-red precipitate was separated by filtration and washed with water. The powder obtained on drying was agitated together with 4.3 ml of a water/ethanol (3:1) mixture for 1 hour at 40° C, whereupon the resulting paste was filtered and dried. There was obtained about 0.9 g of an orange-red powder containing (−) 2-dehydro-emetine, BiI_3 and HI in a proportion of 1:1.41:1.05.

Gelatin capsules which are resistant against gastric juice were manufactured using the complex obtained according to Example 1 as the active material. Each 190 mg capsule contained 51.53 mg of active material admixed with 123.47 mg of talc. The lacquer made up the difference.

WHAT WE CLAIM IS:—

1) Bismuth iodide complexes of 2-dehydro-emetine having the empirical formula $C_{29}H_{38}O_4N_2$, $xBiI_3$,yHI in which x and y have values ranging from 0.7 to 2.0.

2) A pharmaceutical preparation comprising a complex set forth in claim 1 in association with a compatible pharmaceutical carrier.

3) A process for the manufacture of the complexes claimed in claim 1, which process comprises reacting 2-dehydro-emetine or an acid addition salt thereof with a bismuth iodide complex salt which contains the anion $[BiI_4]^-$.

4) A process in accordance with claim 3, wherein a salt of a weak acid is used as the acid addition salt.

5) A process in accordance with claim 4, wherein said salt is the acetate.

6) A process in accordance with claim 5, wherein the acetate is formed *in situ* by introducing 2-dehydro-emetine in the form of the free base into acetic acid.

7) A process in accordance with any one of claims 3 to 6 inclusive, wherein an alkali-metal bismuth iodide complex salt is used.

8) A process in accordance with claim 7, wherein said complex salt is potassium bismuth iodide.

9) A process for the manufacture of the complexes claimed in claim 1, substantially as described with reference to Examples 1 to 3.

10) Complexes as claimed in claim 1, when manufactured by the process claimed in any one of claims 3 to 9 inclusive.

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